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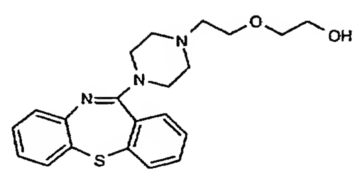
PREPARATION OF QUETIAPINE

The present invention is directed to a new method for the preparation of quetiapine. Further objects of the invention are novel intermediates useful in the process according to the invention.

BACKGROUND OF THE INVENTION

11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f]-1,4-thiazepine (I) is a well established drug substance known under the INN name quetiapine.



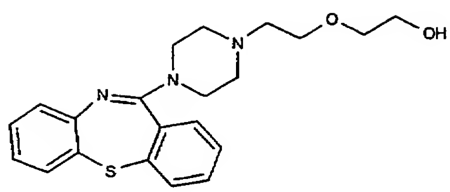
I

It is used as hemifumarate salt as an antipsychotic or neuroleptic.

Several methods for the preparation of quetiapine are known, as disclosed in e.g. GB 8607684, GB 8705574, and WO 01/55125. The known methods include reacting a halo derivative (e.g. iminochloride) of dibenzo[b,f][1,4]-thiazepin-11(10-H)-one with 1-(hydroxyethoxyethyl)piperazine; reacting the aforementioned halo derivative with piperazine and reacting the resulting intermediate with a haloethoxyethanol; and reacting a haloethylpiperazinylthiazepine derivative with ethylene glycol.

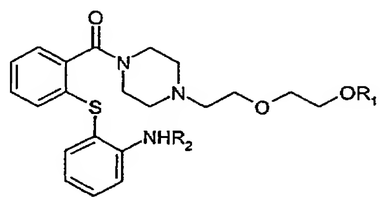
SUMMARY OF THE INVENTION

The present invention is directed to a method for the preparation of the compound of formula I or a salt thereof



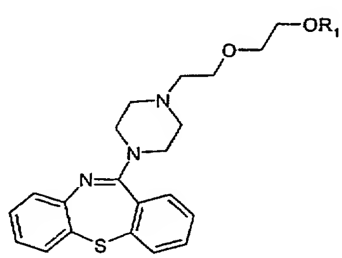
I

by cyclization of a compound of formula II or a salt thereof



II

wherein R_1 is a hydroxyl protecting group selected from the group consisting of acetyl, benzoyl, pivaloyl, benzyl, 4-methoxybenzyl, allyl, tetrahydropyranyl, silyl, alkyl carbonate, aryl carbonate, aralkyl carbonate, benzyl carbonate, allylsulfonyl, benzylsulfonyl, toluenesulfonyl and R2 is H or a suitable amino protecting group , e.g. acetyl, pivaloyl or benzyl to produce a compound of formula III or a salt thereof



III

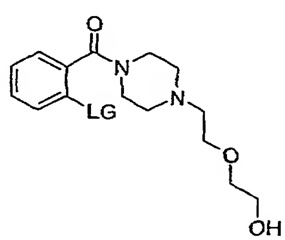
in which R_1 is defined as above, which on removal of R_1 yields compound I or a salt thereof.

The compound of formula I or a salt thereof can be further reacted to a pharmaceutically acceptable salt thereof, e.g. hemifumarate.

The inventors have surprisingly noticed that the thiazepine ring closure takes place in Vilsmeier reaction conditions even though both hydroxyl and aniline moiety are acetate protected. To the knowledge of the inventors this kind of reaction is previously unknown and offers a novel method for the preparation of quetiapine and other thiazepines.

Selective hydroxyl group protection of intermediate V is difficult to perform. For example, if acetylation is used, a mixture of mono O-acetate and diacetylated compounds is frequently obtained. The possibility of using the diacetylated compound in ring closure reaction step makes the whole process more easy to work. It is also possible to use mixtures of mono O-acetate and diacetate in the ring closure step.

The invention also includes the novel intermediate compounds II defined above and salts thereof, and further compounds of formula IV and salts thereof



IV

wherein LG is a leaving group, e.g. halogen, diazonium, trifluoromethyl, O-trifluoromethane-sulfonyl, O-p-toluenesulfonyl or O-methanesulfonyl, preferably halogen or diazonium.

Compounds I to VII can also be used and prepared as suitable salts thereof, e.g as acetates or hydrochlorides.

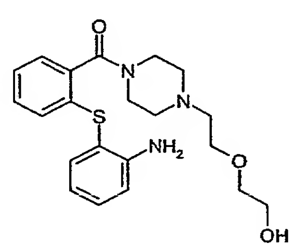
DISCLOSURE OF THE INVENTION

According to the present invention, cyclization of compound II yields compound III, which on hydroxyl deprotection yields the target compound, quetiapine, which can be further reacted to a pharmaceutically acceptable salt, e.g. hemifumarate.

Preferably, the ring closure takes place under Vilsmeier conditions in the presence of a chlorinating agent and optionally in the presence of a strong tertiary amine base. Possible chlorinating agents include but are not limited to $POCl_3$, $SOCl_2$, PCl_3, PCl_5, $COCl_2$, and $(COOCl)_2$; preferably, the reagent is $POCl_3$. The chlorinating agent may be used in large excess but preferably 4 to 5 molar equivalent is used. Possible bases include triethylamine, di-isopropylethylamine, DABCO, N,N-dimethylamine and triethylenediamine. The reagent can act as a solvent, but also a co-solvent selected e.g. from toluene, xylene, acetonitrile and chlorinated hydrocarbons can be used. Preferred co-solvents, if used, are toluene, acetonitrile and mixtures of these. Carboxylic acids, e.g. acetic acid, water, inorganic acids and alcohols can be used as beneficial additives in this reaction. The reaction temperature and the duration are dependent on the solvent used; advantageously reflux temperature or a temperature close thereto is used. For example, the temperature may be in the range 50 - 120 °C and the reaction time in the range of 0,5 to 6 h.

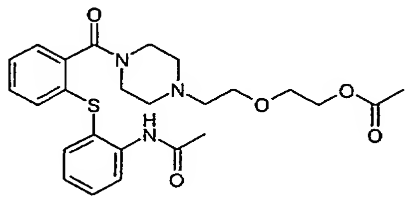
Compound III may be deprotected by saponification using a suitable base in an alcohol to give quetiapine. Preferably, the reaction takes place with aqueous alkali metal hydroxide in methanol, ethanol or 2-propanol. Quetiapine base can be converted to a pharmaceutically acceptable salt, e.g. hemifumarate by methods known in the art and purified further e.g. by crystallization from a suitable solvent.

R_1 and R_2 may be introduced individually or in one step by reaction of intermediate V or a salt thereof with one or more reagents reactive towards amino and/or hydroxyl groups.



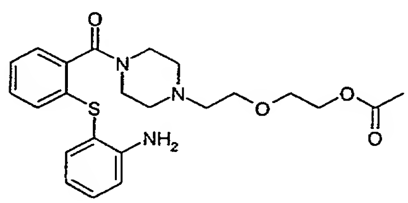
V

According to a preferable embodiment of the present invention, compound II or a salt thereof is represented by the diacetyl compound VI or a salt thereof, which is obtained by acetylation of intermediate V or a salt thereof.



VI

According to another embodiment of the present invention, compound II or a salt thereof is represented by the mono-, i.e. O-acetylated compound VII or a salt thereof,



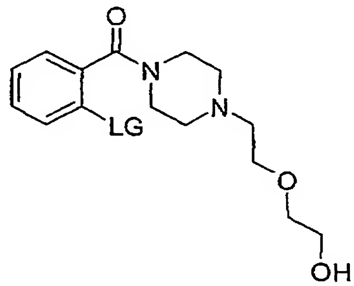
VII

obtainable under non-exhaustive acetylation conditions. Acetylation may also result in a mixture of mono- and diacetylated product, which may be used in place of the pure intermediates.

Acetylation may be carried out in a mixture of acetic acid and acetic anhydride or acetyl chloride with or without cosolvent. Possible cosolvents include ethers, esters, aromatic hydrocarbons, chlorinated hydrocarbons, ketones and acetonitrile. The temperature may be in the range of 0-120 °C, and the reaction time 1-20 h. If the diacetylated compound is prepared, acetylation reagent is used with 1 to 3 fold excess.

Intermediate V or a salt thereof may be obtained by coupling of 2-aminothiophenol with intermediate IV or a salt thereof, which can be used either isolated or a crude

product from the reaction between compound of formula VIII or a salt thereof and 1-[2-(hydroxyethoxy)-ethyl]-piperazine.



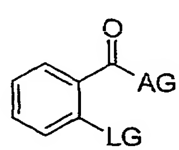
IV

LG represents a leaving group, e.g. halogen, diazonium, trifluoromethyl, O-p-toluenesulfonyl or O-methanesulfonyl. The reaction is carried out optionally in the presence of a metal catalyst, a base and a ligand compound in a solvent.

Useful metal catalysts include palladium, nickel and copper compounds. Preferable catalysts are copper iodide and copper bromide. Useful solvents include water, ionic liquids, alcohols, polyethylene glycol, N,N-dimethylformamide, toluene, acetonitrile and mixtures thereof. Preferably, the solvent is water or an alcohol or the mixture of these. The base present may be organic or inorganic; preferably, the base is potassium carbonate. The ligand compound may be a diol, a diamine, an aminoalcohol or EDTA. Preferably, if the ligand compound is used, it is ethylene glycol.

The reaction temperature and duration are dependent on the solvent used. For example, the temperature range may be 50 -120 °C and the reaction time 1 - 20 h.

Intermediate IV may be prepared by reaction of 1-[2-(hydroxyethoxy)-ethyl]-piperazine with a compound of formula VIII



VIII

wherein LG is defined as above and AG is a typical carboxylic acid activating group, e.g. halogen, alkyloxy, aryloxy, mixed aliphatic or aromatic anhydride, azide or carbodiimide.

The reaction may be carried out in the presence of a base. Possible solvents include water, aromatic hydrocarbons, chlorinated hydrocarbons, esters and ethers or their mixtures with water. Triethylamine, other tertiary amines or inorganic bases may be used. Preferably the reaction is carried out in water without a base. The reaction takes place in ambient temperature, but any temperature between 0- 100 °C may be used.

The following examples merely illustrate the invention and they are not to be construed as limiting.

EXAMPLES

Example 1.

a. {4-[2-(2-hydroxy-ethoxy)ethyl- piperazin-1-yl}-(2-iodophenyl)- methanone
2-iodobenzoic acid (20 g, 0,081 mol), toluene (20 ml) and thionyl chloride (30 ml, 0,41 mol) were charged into a reaction flask. The mixture was stirred and refluxed for 11 h. Toluene (40 ml) was added and the solvent and excess of thionylchloride were distilled off under reduced pressure. The process was repeated with 20 ml of toluene. The residue of 2-iodobenzoyl chloride was dissolved into THF (20 ml). 1-[2-(hydroxyethoxy)-ethyl]-piperazine (14,1 g, 0,081 mol), THF (100 ml), water (50 ml) and triethylamine (12,3ml) were added into a reaction flask and stirred at icewater bath temperature. The previously prepared 2-iodobenzoyl chloride THF solution was slowly added to the reaction mixture. The temperature was kept below 20 °C during the addition. The reaction mixture was allowed to warm to room temperature and stirred 2 h at ambient temperature. 50 ml of water was added and THF was removed by distillation. The pH of the solution was checked and adjusted to 9-10. The water was extracted three times with dichloromethane (50 ml). The combined organic phase was evaporated yielding {4-[2-(2-hydroxy-ethoxy)ethyl-

piperazin-1-yl}-(2-iodophenyl)- methanone as a yellowish oil, which was used without further purification. Yield 31 g.
^{1}H NMR ($CDCl_3$): 2.42 (1H, m), 2.63 (5H, m), 3.25 (2H,m), 3.59 (2H,m), 3.68 (4H, m), 3.90 (3H, m), 7.06 (1H, t), 7.18 (1H, d), 7.40 (1H, t), 7.83 (1H, d).
^{13}C NMR ($CDCl_3$): 41.3, 45.9, 46.6, 52.7, 53.4, 57.7, 61.9, 67.8, 72.4, 92.5, 127.0, 128.4, 130.2, 139.2, 142.1, 169.1.

b. 2-(2-amino-phenylsulfanyl)-phenyl-{4(2-(2-hydroxyethoxy)ethylpiperazin-1-yl} methanone

{4-[2-(2-hydroxy-ethoxy)ethyl- piperazin-1-yl}-(2-iodophenyl)- methanone (10 g, 0,025 mol) was dissolved in isopropanol (50 ml) and ethylene glycol (2,5 ml). CuI (0,24 g , 5 mol %) and K_2CO_3 (6,9 g) were added to the reaction mixture. The reaction vessel was flushed with nitrogen, and 2-aminothiophenol (3,4 g, 0,028 mol) was added under a nitrogen atmosphere. The reaction mixture was refluxed overnight (12-18 h). Solid material was filtered off and the solvent was evaporated. The residue was dissolved in ethyl acetate (100 ml) and washed once with 1 M NaOH (25 ml). Water (100 ml) was added and the pH was adjusted to 5 with dilute acetic acid. The organic layer was washed once with water (50 ml) and the water phases were combined. The pH of the water was adjusted to 10-11 with 1 M NaOH and the basic water phase was extracted twice with ethyl acetate (100 ml). The combined organic phases were evaporated to afford [2-(2-amino-phenylsulfanyl)-phenyl-{4(2-(2-hydroxyethoxy)ethyl]piperazin-1-yl} methanone as a dark red oil, yield 8,8 g.
^{1}H NMR ($CDCl_3$): 2.51 (2H, s), 2.64 (4H, m), 3.36 (2H, m), 3.60-3.71 (6H, m), 3.90 (2H, s, broad), 4.46 (2H, s), 6.73 (2H, m), 6.94 (1H, m), 7.15-7.29 (4H, m), 7.45 (1H, d).
^{13}C NMR ($CDCl_3$): 41.4, 46.8, 52.9, 53.7, 57.8, 61.9, 67.8, 72.4, 113.8, 115.4, 118.2, 126.1, 126.4, 128.4, 129.5, 131.3, 133.9, 135.7, 137.4, 149.3, 168.5.

Steps a and b can also be performed in one pot without isolation of the intermediate made in step a.

c. [2-(2-acetamino-phenylsulfanyl)-phenyl]-{4(2-(2-acetoxyethoxy)ethyl]-piperazin-1-yl} methanone

[2-(2-amino-phenylsulfanyl)-phenyl]-{4(2-(2-hydroxyethoxy)ethyl]piperazin-1-yl} methanone (10,7 g, 0,027 mol) was dissoved in ethyl acetate (50 ml) and triethylamine (7,4 ml) was added into reaction mixture. Acetic anhydride (7,6 ml, 0,081mol) was slowly added to the reaction mixture at room temperature. After 4 h, the reaction mixture was evaporated to give a dark blue oil which was dissolved in ethyl acetate (50 ml) and washed with 2x25 ml saturated $NaHCO_3$ solution and once with brine. The organic phase was evaporated to give a brown oil (10,9 g). The residue of [2-(2-acetamino-phenylsulfanyl)-phenyl-{4(2-(2-acetoxyethoxy)ethyl]-piperazin-1-yl} methanone was used further without purification.

^{1}H NMR ($CDCl_3$): 2.04 (3H, s), 2.08 (3H, s), 2,49 (2H,m), 2.66 (4H,m), 3.29 (2H, s,broad), 3.66 (3H, m), 3,90 (1H, m), 4.21 (2h, d), 7,07 (1H, t),7,08-7,39 (3h,m), 7,61 (1H, t), 7,63 (1H, d), 8,34 (1H, d), 8,80 (1H, s).

^{13}C NMR ($CDCl_3$): 21.0, 24.3, 41.7, 47.0, 53.1, 53.8, 63.4, 68.8, 69.0, 121.3, 122.2, 123.8, 126.1, 127.5, 130.0, 130.6, 131.5, 132.8, 136.3, 137.0,140.2, 168.7, 169.6, 170.9.

d. 11-(4-[2-(2-acetyloxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f]-1,4-thiazepine

[2-(2-acetamino-phenylsulfanyl)-phenyl-{4(2-(2-acetoxyethoxy)ethyl]piperazin-1-yl} methanone (2 g, 0,0041 mol) was dissolved in $POCl_3$ (5 ml) and stirred at room temperature for 30 min. The mixture was slowly heated to reflux and refluxed for 3 h. Excess of $POCl_3$ was evaporated and water 50 ml and methanol (5 ml) were carefully added to the residue. The mixture was stirred at room temperature until all material was dissolved. The pH of the water was adjusted to 10-11 by addition of NaOH followed by extraction with toluene 2x50 ml. The organic layer was separated and evaporated to give a dark residue of 11-(4-[2-(2-acetyloxy-ethoxy)ethyl]- 1-piperazinyl]dibenzo[b,f]-1,4-thiazepine (1,53 g).

^{1}H NMR (CDCl3): 2.06 (3H, s), 2.52-2.67 (6H, m), 3.46-3.68 (8H, m), 4.21 (2H, m), 6.68 (1H, t), 7.06 (1H, d), 7.16 (1H, t), 7.31 (3H, m), 7.38 (2H, d), 7.50 (1H, d).

^{13}C NMR (CDCl3): 20.9, 46.7, 47.6, 53.4, 57.8, 63.4, 68.9, 70.0,122.8, 125.3, 128.0, 128.2, 129.0, 129.1, 130.7, 132.1, 132.2, 134.2, 140.0, 148.9, 160.7, 171.0.

e. Quetiapine base

The residue of 11-(4-[2-(2-acetyloxyethoxy)ethyl]- 1-piperazinyl]dibenzo[b,f]-1,4-thiazepine (7,8 g) was dissoved in ethanol (50 ml) and 1M NaOH solution (55 ml) was added. The mixture was stirred at room temperature for 30 min. The product was extracted into toluene (2 x 100 ml). Evaporation of the toluene phase gave quetiapine base (6,9 g).

Example 2

Steps a and b as in example 1.

c. Dihydrobromide salt of [2-(2-amino-phenylsulfanyl)-phenyl-{4(2-(2-hydroxyethoxy)ethyl]piperazin-1-yl} methanone

The evaporation residue of [2-(2-amino-phenylsulfanyl)-phenyl-{4(2-(2-hydroxyethoxy)ethyl]piperazin-1-yl} methanone (example 2) (7,5 g , 0,019 mol) was dissolved in 2-propanol (40 ml). The mixture was heated to 80 °C, and a 34% solution of HBr in AcOH (9,3 g , 2,1 mol) was slowly added to the almost refluxing mixture. The solution was slowly allowed to reach room temperature and finally kept 30 min in an ice water bath. The precipitated product was filtered and washed with cold 2-propanol to afford the dihydrobromide as a pale grey powder (7.4 g).

d. [2-(2-amino-phenylsulfanyl)-phenyl-{4(2-(2-acetoethoxy)ethyl]piperazin-1-yl} methanone x 2 HBr

Compound [2-(2-amino-phenylsulfanyl)-phenyl-{4(2-(2-hydroxyethoxy)ethyl]piperazin-1-yl} methanone x 2 HBr (5 g, 0,009 mol) was dissoved in acetic acid and heated until all solid material was dissolved. Acetic anhydride (0,96 ml, 0,010mol) was slowly added to the warm reaction mixture at ca. 50 °C. The reaction was continued for 2 h at constant temperature. After 2 h the reaction mixture was evaporated to give a dark blue oil (7.3 g) which still contained some acetic acid. HPLC from the residue showed 95 % pure [2-(2-amino-phenylsulfanyl)-phenyl-{4(2-(2-acetoxyethoxy)ethyl]piperazin-1-yl} methanone x 2 HBr, and it was used without further purification.

Ring closure and deprotection may be carried out in accordance with steps d and e of example 1.